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ENCLOSURES (check all that apply)

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- [x] **APPELLANTS' REPLY BRIEF UNDER 37 C.F.R. §1.193(b)(1)** *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
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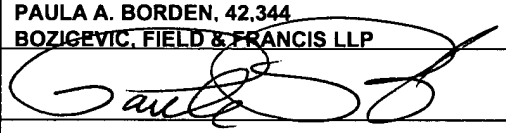
Signature	
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APPELLANTS' REPLY BRIEF UNDER 37 C.F.R. §1.193(b)(1)	Attorney Docket Confirmation No.	UCAL-121 2429
	First Named Inventor	Y. Huang
	Application Number	09/544,910
Address to: **Appeal Brief - Patents** Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Filing Date	April 7, 2000
	Group Art Unit	1642
	Examiner Name	S.L. Rawlings
	Title	*Methods and compositions for use in the treatment of hyperlipidemia*

Sir:

This Reply Brief is submitted in response to the Examiner's Answer dated August 12, 2003, for which a two-month period for response was given, making this response due on or before October 12, 2003. Accordingly, this response is timely filed.

In view of the remarks set forth below, reconsideration and allowance are respectfully requested.

I. REMARKS

Status of rejections

The rejection of claims 1, 4-8, and 11 under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement, has been withdrawn.

The rejection of claims 5 and 77 under 35 U.S.C.§121, second paragraph, as allegedly indefinite, has been withdrawn.

The rejection of claims 1, 4-8, and 11 under 35 U.S.C.§112, first paragraph, as allegedly lacking written description, has been maintained.

The rejection of claims 1, 4-8, and 11 under 35 U.S.C.§102(b), as allegedly anticipated by Ditschuneit et al. ((1992) *J. Int'l. Med. Res.* 20:197-210; "Ditschuneit") as evidenced by Pedreño et al. ((2000) *Metabolism* 49:942-949; "Pedreño") and Durrington et al. ((1998) *Atherosclerosis* 138:217-225; "Durrington") has been maintained.

The rejection of claims 1, 4-8, and 11 under 35 U.S.C.§102(b) as allegedly anticipated by Yoshino et al. ((1989) *Atherosclerosis* 75:67-72; "Yoshino") has been maintained.

The rejection of claims 1, 4-8, and 11 under 35 U.S.C.§102(b) as allegedly anticipated by Connor et al ((1993) *Ann. N.Y. Acad. Sci.* 683:16-34; "Connor") has been maintained.

The rejection of claims 1, 5, 6, and 11 under 35 U.S.C.§102(b) as allegedly anticipated by Kasiskie et al. ((1990) *Am. J. Kidney Dis.* 15:8-15; "Kasiskie") as evidenced by Wyne et al. ((1989) *J.*

Biol. Chem. 264:16530-16536; "Wyne") has been maintained.

Rejection of claims 1, 4-8, and 11 under 35 U.S.C.§112, first paragraph

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification contains a written description of the invention according to 35 U.S.C. § 112, first paragraph.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). Thus, the test for whether a claimed invention is adequately described has often been stated as whether or not one of skill in the art would have understood from the specification that an applicant possessed the claimed subject matter when the specification was filed. *See, e.g., Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575, 227 U.S.P.Q. (BNA) 177, 179 (Fed. Cir. 1985). Whether the specification meets the written description requirement for the claimed invention is a question of fact. *Vas-Cath,* 935 F.2d at 1563, 19 U.S.P.Q.2d (BNA) at 1116. What is required to satisfy the written description requirement depends on the nature of the invention claimed. *In re DiLeone*, 436 F.2d 1404, 1405, 168 U.S.P.Q. (BNA) 592, 593 (C.C.P.A. 1971).

In the Appeal Brief filed on April 25, 2003, Appellants explained that at least three different types of agents can be used in the claimed methods, as follows:

1) The specification states that **small molecules** are useful for reducing plasma active apoE. Specification, page 10, lines 1-17. The specification states that the agent may be an apoE inhibitor. Specification, page 10, lines 2-6.

2) The specification states that **antisense molecules** are useful for reducing expression of apoE. Specification, page 14, line 12 to page 15, line 14. The nucleotide sequences of mRNA encoding apoE were known as of the effective filing date of the instant application. For example, the specification

provides the GenBank accession numbers providing mRNA sequences of human apoE2, apoE3, and apoE4. Specification, page 15, lines 7-10. Because the nucleotide sequences of apoE mRNAs are known, the sequences of antisense are also known, and need not be provided in the specification. Applicants note that it is well established that a "patent need not teach, and preferably omits, what is well known in the art." MPEP §2164.01. Because the nucleotide sequence of genes encoding apoE, e.g., apoE3 were known, those skilled in the art would reasonably expect that one could use antisense technology to reduce apoE expression. Thus, those skilled in the art would have recognized that Appellants were in possession of the claimed invention, where the agent is an antisense molecule.

3) The specification states that **ribozymes** are useful for reducing expression of apoE. Specification, page 16, lines 8-16. As discussed above, the nucleotide sequence of mRNA encoding apoE were known as of the effective filing date of the instant application. Because the nucleotide sequence of genes encoding apoE, e.g., apoE3 were known, those skilled in the art would reasonably expect that one could use ribozyme technology to reduce apoE expression. Therefore, those skilled in the art would have recognized that Appellants were in possession of the claimed invention, where the agent is a ribozyme.

As one example of an agent suitable for use in the claimed methods, Appellants discussed antisense molecules. Appellants pointed out that Charpentier et al. ((2000) *Biochemistry* 39:16084-91, a copy of which was provided along with the response to the Office Action mailed August 9, 2001) have already demonstrated that antisense technology can be used to reduce apoE expression. Charpentier discloses the use of apoE antisense to reduce apoE gene expression in eukaryotic cells. The Examiner's Answer stated that Charpentier is not prior art. The fact that Charpentier was published after the instant application was filed does not negate the fact that Charpentier supports the contention that those skilled in the art would recognize that Appellants had, at as of the filing date of the instant invention, possession of the claimed invention. Charpentier was published about 18 months after the priority date of the instant invention. There were hundreds of papers published before the priority date of the instant application describing use of antisense molecules to reduce expression of a wide variety of genes. Charpentier used nothing more than techniques and information that were widely available to those of ordinary skill in the art as of the priority date of the instant application. Charpentier is but one more example of the use of antisense to reduce gene expression. Charpentier thus provides further support for the fact that those skilled in the art could, as of the priority date of the instant application, use agents

such as antisense to reduce expression of apoE, and that therefore those skilled in the art would recognize that Appellants had possession of the invention as claimed as of the priority date of the instant application.

The Examiner's Answer states that supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying necessary and essential teachings. Charpentier is not being relied upon to supply necessary and essential teachings. There is no information in Charpentier that was not available to those skilled in the art as of the priority date of the instant application. All that would be required to carry out a claimed method using antisense would be knowledge of the sequence of the apoE gene; and general knowledge about how to generate antisense RNA molecules. As Appellants pointed out previously, the nucleotide sequence of the apoE gene was known as of the priority date of the instant application. Furthermore, there was ample knowledge in the art as of the priority date of the instant invention about how to generate antisense and use same, and the skill level of those of ordinary skill in the art of antisense and use of same was very high.

The Examiner's Answer states that in view of "the preponderance of factual evidence of record, and contrary to Appellants' assertions, the claimed invention would not have been enabled by disclosures of the prior art at the time the application was filed..." Examiner's Answer, page 13. However, it is noted that the rejection is a written description rejection, not an enablement rejection, and indeed the enablement rejection has been withdrawn. Furthermore, there does not appear to have been a "preponderance of evidence" provided by the Examiner at any time during prosecution of the instant application.

The position articulated by the Examiner with respect to antisense technology is inconsistent with the U.S. Patent & Trademark's position on antisense technology.

The Examiner's Answer cited "*The Guidelines for Examination of Patent Applications under the 35 U.S.C.§112, paragraph 1, "Written Description" Requirement*" ((January 5, 2001) *Fed. Reg.* 66:1099-1111) ("Written Description Guidelines"), which states that possession may be shown in a variety of ways. The Written Description Guidelines reiterate much of the text of the guidelines published in "The Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, paragraph 1 "Written Description" Requirement," (*Federal Register* (Dec. 21, 1999) Vol. 64 (No.

244):71427-71440) ("Revised Guidelines"). The Written Description Guidelines Training Materials, which were provided to patent examiners for determining compliance with the written description requirement according to the Revised Guidelines, and which were posted on the U.S. Patent & Trademark Office web site on March 1, 2000, provide an example of an analysis of a claim to an antisense oligonucleotide. In the example, the specification disclosed an mRNA sequence, SEQ ID NO:1, which encodes human growth hormone, and the specification stated that the invention included antisense molecules that inhibit production of human growth hormone. In the analysis, a claim to an antisense oligonucleotide complementary to SEQ ID NO:1 was deemed to be adequately described because the procedures for making oligonucleotide fragments of the SEQ ID NO:1 complement are conventional, **the procedures for screening for antisense activity are also conventional**, and the **general level of knowledge and skill in the art is high**. A similar analysis and conclusion applies to the instant claims. The U.S. PTO's Written Description Guideline Training Materials were meant to assist examiners in applying the Revised Guidelines issued on December 21, 1999. Because the April 22, 1999 priority date is before the December 21, 1999 Revised Guidelines, it is clear that the U.S. PTO's position regarding antisense, as articulated in The Written Description Guidelines Training Materials, was that ***antisense technology was conventional and routine*** as of the April 12, 1999 priority date of the instant application.

As discussed previously, the nucleotide sequence of the apoE gene was known as of the priority date of the instant application, and therefore there was no need to disclose same. Nevertheless, the specification points to the GenBank Accession No. where the mRNA sequence of human apoE4 can be found. Specification, page 15, lines 8-10. As the Written Description Guidelines Training Materials states, methods for making oligonucleotide fragments complementary to a known mRNA sequence are conventional, the procedures for screening for antisense activity are also conventional, and the general level of knowledge and skill in the art is high. Accordingly, the instant claims are adequately described.

The Examiner's Answer reiterated the contention that the teachings of Sohail, Pierce, and Lesoon-Wood indicate the unpredictability of antisense technology. However, as discussed in the Appeal Brief, Sohail states that empirical approaches to identifying an antisense nucleic acid that hybridizes with a given sense nucleic acid are successful; Pierce merely discusses predicting the optimal sequence of a ribozyme nucleic acid, and discusses a method for identifying ribozymes that are effective in modulating gene expression; and Lesoon merely discusses an isolated problem with antisense. The

Examiner has completely ignored the fact that, as discussed in the Appeal Brief, the overwhelming body of literature points to many successes with antisense technology. Furthermore, as discussed above, the Examiner's position with regard to the state of antisense technology appears to be inconsistent with that of the U.S. PTO.

The case law cited by the Examiner does not support a written description rejection of the instant claims.

The Examiner cited *Enzo Biochem. Inc. v. Calgene, Inc.*, 52 USPQ2d 1129 (Fed. Cir. 1999), *Fiers v. Sugano*, 984 F.2d 1164, 25 U.S.P.Q.2d (BNA) 1601 (Fed. Cir. 1993), and *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 U.S.P.Q.2d (BNA) 1016 (Fed. Cir. 1991), in support of the written description rejection of the appealed claims. None of this case law supports the rejection of the appealed claims.

Enzo Biochem. Inc. v. Calgene, Inc., 52 USPQ2d 1129 (Fed. Cir. 1999)

The Examiner's Answer stated that the courts have determined that antisense technology is highly unpredictable, citing *Enzo Biochem. Inc., v. Calgene, Inc.* 52 USPQ2d 1129 (CAFC, 1999); "*Enzo*." However, *Enzo* does not support a conclusion that the instant claims lack written description. Indeed, *Enzo* discusses **enablement**, not written description. The situation being analyzed in *Enzo* is very different to the instant claims, and it is thus doubtful that *Enzo* applies at all to the instant case. In *Enzo*, the court found that claims encompassing the practice of antisense in both prokaryotic and eukaryotic cells were too broad and not supported by an enabling disclosure, which disclosure taught the application of antisense technology in regulating three genes in the prokaryote *E. coli*. The instant claims are not directed to "a prokaryotic or eukaryotic cell containing a non-native DNA construct, which construct produces an RNA which regulates the function of a gene," as did the patents under review in *Enzo*. Instead, the instant claims recite use of an agent that reduces expression of apoE, for which the sequence was known as of the effective filing date.

Furthermore, the court in *Enzo* reviewed the Wands factors, which include a review of the predictability or unpredictability of the art *at the time the application was filed.* The court in *Enzo* concluded that the antisense was a highly unpredictable technology; however, the patents in question, namely U.S. Patent Nos. 5,190,031 and 5,208,149, claimed an earliest filing date of October 20, 1983. **This is more than 15 years before the April 12, 1999 priority date of the instant application**. The predictability of the antisense technology as of October 20, 1983 is not relevant to the instant

application. Instead, the written description requirement stipulates that the inventor demonstrate possession of the subject matter *as of the filing date of the application.* As stated in the Written Description Guidelines, a review of compliance with the written description requirement **is conducted from the standpoint of one of skill in the art at the time the application was filed, and should include a determination of the field of the invention and the level of skill and knowledge in the art.** As discussed in the Appeal Brief and during prosecution of the instant case, the skill and knowledge in the art of antisense as of the priority date of the instant application was high. Accordingly, *Enzo* is irrelevant to a determination of compliance with the written description requirement of the instant claims. Finally, as noted above, the U.S. PTO has taken the position that antisense technology is routine and conventional.

Fiers v. Sugano, 984 F.2d 1164, 25 U.S.P.Q.2d (BNA) 1601 (Fed. Cir. 1993)

Fiers does not support a written description rejection of the instant claims. *Fiers* reports an award of priority to Sugano in a three-way interference proceeding between Revel, Sugano, and Fiers. 984 F.2d at 1166, 25 U.S.P.Q.2d (BNA) at 1602. In this case, the Federal Circuit applied the holding in *Amgen* to an interference case where three parties (Fiers, Revel, and Sugano) claimed patent rights to the DNA encoding human fibroblast beta interferon (IFN-β). Fiers asserted priority based on his conception of a method for isolating the IFN-β DNA in 1979 or early 1980, coupled with due diligence towards a constructive reduction to practice on April 3, 1980. *Id* Before he isolated the DNA, Fiers had disclosed his method to two American scientists, both of whom submitted affidavits that Fiers' method would have allowed a person of ordinary skill in the art to isolate the IFN-β DNA sequence without undue experimentation. *Id.* Fiers asserted that the stringent written description requirement set forth in *Amgen* only applied when the disclosed method for isolating a DNA sequence could not easily be carried out by one of ordinary skill in the art. *Id.* at 1169. The instant claims are not drawn to DNA sequences. *Fiers*, therefore, cannot be used to assert that the subject matter of the appealed claims are not adequately described. Furthermore, as stated in the Written Description Guidelines, a review of compliance with the written description requirement is conducted from the standpoint of one of skill in the art at the time the application was filed, and should include a determination of the field of the invention and the level of skill and knowledge in the art. The *Fiers* decision was made based on an analysis of written description in an application filed more than 20 years ago.

Amgen, Inc. v. Chugai Pharmaceutical, Co.

In *Amgen, Inc. v. Chugai Pharmaceutical,* 927 F.2d 1200, 18 U.S.P.Q.2d (BNA) 1016 (Fed. Cir. 1991), *Co.*, the Federal Circuit considered an Amgen patent issued on October 27, 1987, which contained claims to the DNA sequence encoding human erythropoietin (EPO). Amgen claimed priority of invention based on isolation of EPO clones in 1983.

Prior to Amgen's cloning of the EPO gene, however, Genetics Institute ("GI") had isolated and purified the EPO protein, and had also disclosed a strategy for obtaining the EPO DNA sequence. *Id.* at 1205. The USPTO issued a patent to GI on June 30, 1987 with claims to the EPO protein itself. *Id.* at 1203. GI did not actually clone the EPO cDNA until August 1984, and began making recombinant EPO using the cDNA shortly thereafter. *Id.* at 1205-06.

The Federal Circuit held that the Amgen patent was not invalidated by GI's earlier-disclosed isolation strategy to obtain the EPO DNA and its sequence, even though this strategy eventually resulted in the actual cloning of the gene by GI. *Id.* at 1206. GI's disclosure of the protein, and a method for isolating and purifying the EPO DNA sequence, was insufficient to constitute actual conception of the DNA encoding EPO. *Id.*

Thus, since GI had not yet cloned the DNA sequence encoding EPO when it filed its patent application, and the specification only suggested a possible method by which to isolate the DNA sequence, GI could not have a mental conception of the EPO DNA sequence at the time the application was filed. *Id.* The court did not invoke the requirement that the actual DNA sequence be disclosed, but only that the DNA be defined in a way to distinguish it from other chemicals along with a description of how to obtain it. *Id.*

In contrast, the appealed claims are not directed to DNA molecules. The appealed claims are directed to a method involving administering agent that reduce the expression of apoE. The instant specification discloses various agents that will accomplish such a reduction. *Amgen*, therefore, cannot be properly applied to assert that the subject matter of the appealed claims are not adequately described. Furthermore, as stated in the Written Description Guidelines, a review of compliance with the written description requirement is conducted from the standpoint of one of skill in the art at the time the application was filed, and should include a determination of the field of the invention and the level of skill and knowledge in the art. The *Amgen* decision was made based on an analysis of written description in an application filed 20 years ago.

Rejections under 35 U.S.C.§102(b)

Claims 1, 4-8, and 11 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ditschuneit et al. ((1992) *J. Int'l. Med. Res.* 20:197-210; "Ditschuneit") as evidenced by Pedreño et al. ((2000) *Metabolism* 49:942-949; "Pedreño") and Durrington et al. ((1998) *Atherosclerosis* 138:217-225; "Durrington"). Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Yoshino et al. ((1989) *Atherosclerosis* 75:67-72; "Yoshino"). Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Connor et al ((1993) *Ann. N.Y. Acad. Sci.* 683:16-34; "Connor"). Claims 1, 5, 6, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Kasiskie et al. ((1990) *Am. J. Kidney Dis.* 15:8-15; "Kasiskie") as evidenced by Wyne et al. ((1989) *J. Biol. Chem.* 264:16530-16536; "Wyne").

The claims recite administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE.

Claims 1 and 5 were amended in the amendment, filed November 8, 2001 and responsive to the August 9, 2001 Office Action, to recite administering an agent that reduces the amount of plasma active apoE "by reducing the expression of apoE."

The May 15, 2002 Office Action asserted that the claims are not limited to a method in which the level of transcription of the gene encoding apoE is reduced, or in which the level of translation of mRNA encoding apoE is reduced. However, the claims recite administering an agent that acts by "**reducing the expression of apoE**." "Reducing the expression of apoE" is an art term understood by those in the field to refer to reducing transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE.

None of the cited art discloses or suggests a method of reducing the plasma level of VLDL in a host, the method comprising administering to the host an effective amount of an agent that reduces the amount of plasma active apoE in said host **by reducing the expression of apoE** by an amount sufficient to reduce VLDL production in the host to reduce the plasma level of VLDL in the host, whereby the plasma level of VLDL in the host is reduced by at least two fold. It does not flow *undeniably and irrefutably* from the express disclosures of the cited references that the agents discussed therein reduce

apoE gene expression.

The Examiner has given the term "reducing the expression of apoE" an overly broad interpretation that is inconsistent with its art-accepted meaning.

The Examiner's Answer states that the claims do not recite a limitation requiring the agent to be administered to the host in an amount effective to reduce the transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE. The Examiner's Answer states that the mechanism by which the agent effects the reduction in expression of apoE is not limited by the claims.

However, the claims clearly require that the agent reduce expression of apoE. Those skilled in the art would understand that an agent that reduces expression of apoE is an agent that reduces transcription and/or translation of an mRNA encoding apoE, and the Examiner has presented no convincing arguments to the contrary.

The Examiner attempts, in the Examiner's Answer, to broaden the phrase "by reducing the expression of apoE" to include reducing the level of post-translational processing of a nascent apoE polypeptide, and a reduction in the level of secretiono f the mature apoE polypeptide. The Examiner has attempted to define gene expression as involving "much more than just transcription and translation," and including transcription, mRNA processing and maturation, nuclear export, translation, post-translational processing, modification, and maturation, intracellular trafficking, and secretion or export." Examiner's Answer, page 23; and bridging sentence, pages 23-24. However, the term "reducing expression of apoE" would not be construed by those skilled in the art to include such functions as "nuclear export, modification, maturation, intracellular trafficking and secretion or export." Such a broad interpretation is not supported by any definition or general understanding of the term "expression of apoE." The Examiner's extremely broad interpretation of "expression of apoE" stretches credulity, and is simply not in keeping with the art-accepted meaning of the phrase.

The Examiner's Answer cited an on-line medical dictionary (cancerweb.ncl.ac.uk) definition of "gene expression" as "The process by which a gene's coded information is converted into the structures present and operating in the cell." However, the Examiner failed to cite the full definition of the term as provided at the cited world wide web site, which definition further stated, "Expressed genes include

those that are transcribed into mRNA and then translated into protein, and those that are transcribed into RNA but not translated into protein (for example, transfer and ribosomal RNAs)."

Other on-line dictionaries define "gene expression" as follows.

1) The on-line dictionary of medical terms at on the world wide web site medterms.com defines "gene expression" thus:

"Gene expression: The translation of information encoded in a gene into protein or RNA."

2) The on-line dictionary of medical terms at the world wide web site books.md/G/dic/geneexpressionregulation.php defines "Gene expression regulation" thus:

"Any of the processes by which nuclear, cytoplasmic, or intercellular factors influence the differential control of gene action **at the level of transcription or translation**. These processes include gene activation and genetic induction." (emphasis added)

3) The on-line dictionary on the world wide web site hyperdictionary.com/dictionary defines "gene expression" thus: "Conversion of the information encoded in a gene first into messenger RNA and then to a protein."

None of the cited art discloses or suggests a method of reducing the plasma level of VLDL in a host, the method comprising administering to the host an effective amount of an agent that reduces the amount of plasma active apoE in said host ***by reducing the expression of apoE.***

The rejections under 35 U.S.C.§102(b) have been discussed in the Appeal Brief in detail.

a) Claims 1, 4-8, and 11 over Ditschuneit as evidenced by Pedreño and by Durrington

The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Ditschuneit is in error. Ditschuneit discusses administering gemfibrozil. Gemfibrozil does not reduce expression of apoE. Therefore, Ditschuneit does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE. Accordingly, Ditschuneit cannot anticipate claims 1, 4-8, and 11.

Gemfibrozil has been reported to increase LDL receptor expression, to reduce triglyceride synthesis, to inhibit human cytochrome P450, and to inactivate acetyl-CoA carboxylase. There is no report in the literature that gemfibrozil reduces expression of apoE. The Examiner's insistence that gemfibrozil affects expression of an apoE gene is purely speculative. The Examiner stated, "If gemfibrozil can affect the expression of one gene associated with the maintenance of particular concentrations of apolipoprotein in the plasma, why not another?" Examiner's Answer, bridging sentence, pages 26-27. It makes no sense biologically or logically to speculate that an agent that increases expression of one gene will affect the expression of another gene.

The Examiner stated that Clavey et al. ((1999) *Cell. Physiol. Biochem.* 9:139-149; "Clavey") reported that fibrates repress apolipoprotein CIII gene expression. The Office Action concluded that the mechanism of gemfibrozil is not limited to increasing LDL receptor expression. However, Clavey does not disclose any effect of gemfibrozil on apoE expression. The Examiner stated, "... Clavey et al. do not disclose the affect [sic] of gemfibrozil upon the transcription of the gene encoding apoE...," thus acknowledging that the art does not teach any effect of gemfibrozil on apoE expression. Examiner's Answer, page 27. The Examiner has provided no basis for extrapolating an effect on apolipoprotein CIII gene expression to an effect on expression of any other gene.

b) Claims 1, 4-8, and 11 over Yoshino

The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Yoshino is in error. Yoshino discusses administering pravastatin. Pravastatin does not reduce expression of apoE. Therefore, Yoshino does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE. Accordingly, Yoshino cannot anticipate claims 1, 4-8, and 11.

As discussed previously, there is evidence that pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. The Examiner stated that 'the fact that pravastatin is an inhibitor of HMG-CoA does not suggest that the inhibition of HMG-CoA does not affect the expression of the gene encoding apoE, or that pravastatin is not also an inhibitor of the expression of apoE." Examiner's Answer, page 30. Again, the Examiner has provided no basis in fact for such an assertion.

The Examiner's Answer stated that Wyne et al. disclose another drug of the same class is capable of attenuating the simulation of transcription of the gene encoding apoE. However, Wyne does not discuss pravastatin, and Wyne does not disclose that pravastatin reduces apoE expression.

c) Claims 1, 4-8, and 11 over Connor

The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Connor is in error. Connor discusses administering dietary n-3 fatty acids. Connor states that dietary n-3 fatty acids caused a reduction in LDL. This is the opposite effect on LDL level that would be expected if n-3 fatty acids acted by decreasing active apoE and would lead one of skill in the art to believe that the mechanism of action is not through a reduction in apoE gene expression. Dietary n-3 fatty acids do not reduce expression of apoE. Therefore, Connor does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE. Accordingly, Connor cannot anticipate claims 1, 4-8, and 11.

As discussed in the Appeal Brief, nothing in Connor teaches that apoE is a target for reducing levels of VLDL production or that reduction of apoE gene expression will cause a reduction in VLDL production. Furthermore, there is nothing that suggests that n-3 fatty acids act to decrease VLDL production by reducing apoE expression, while there is evidence that n-3 fatty acids act through a different mechanism. As noted above, if the cited agent decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE. Huang teaches that increased apoE results in normal or decreased LDL levels; however, Connor states that dietary n-3 fatty acids caused a reduction in LDL. This is the **opposite effect** on LDL level that would be expected if n-3 fatty acids acted by decreasing active apoE by decreasing gene expression, and would lead one of skill in the art to believe that the mechanism of action is not through apoE.

d) Claims 1, 5, 6, and 11 over Kasiskie

The rejection of claims 1, 5, 6, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Kasiskie is in error. Kasiskie discusses administering lovastatin. Lovastatin does not reduce apoE gene expression. Therefore, Kasiskie does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by

reducing the expression of apoE. Accordingly, Kasiskie cannot anticipate claims 1, 5, 6, and 11.

There is no evidence in Kasiskie that lovastatin acts to decrease plasma VLDL levels by reducing expression of apoE. As the Examiner acknowledged, lovastatin is an inhibitor of HMG-CoA reductase. Furthermore, as discussed above, Wyne does not disclose that lovastatin reduces apoE expression.

II. CONCLUSION

Appellants present evidence that the claims comply with the written description requirement of 35 U.S.C.§112, first paragraph. Appellants present evidence that none of the cited art anticipate the claimed invention under 35 U.S.C.§102(b). Additional arguments have already been presented, both in responses to Office Actions during the course of prosecution, as well as in Appellants' Brief. In view of the remarks set forth above, and those already of record, Appellants respectfully request that the rejection of claims 1, 4-8, and 11 be withdrawn, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL121.

Respectfully submitted,
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